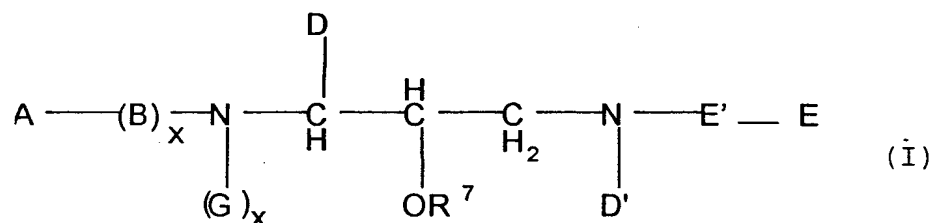


CLAIMS

We claim:

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

E' is -CO- or -SO₂-;

A is selected from H; Ht; -R¹-Ht; -R¹-C₁-C₆ alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂, -SO₂-R² or -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;

each R¹ is independently selected from -C(O)-, -S(O)₂-, -C(O)-C(O)-, -O-C(O)-, -O-S(O)₂-, -NR²-S(O)₂-, -NR²-C(O)- or -NR²-C(O)-C(O)-;

each Ht is independently selected from C₃-C₇ cycloalkyl; C₅-C₇ cycloalkenyl; C₆-C₁₄ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, O, or S; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN,

$-\text{CO}_2\text{R}^2$, $-\text{C}(\text{O})-\text{N}(\text{R}^2)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})\text{O}-\text{R}^2$, $-\text{C}(\text{O})-\text{R}^2$, $-\text{S}(\text{O})_n-\text{R}^2$, $-\text{OCF}_3$, $-\text{S}(\text{O})_n-\text{Q}$, methylenedioxy, $-\text{N}(\text{R}^2)-\text{S}(\text{O})_2(\text{R}^2)$, halo, $-\text{CF}_3$, $-\text{NO}_2$, Q , $-\text{OQ}$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{R}^7$, $-\text{N}(\text{R}^2)(\text{R}^7)$ or $-\text{N}(\text{R}^7)_2$;

each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O , N , or S ; wherein Q is optionally substituted with one or more groups selected from oxo, $-\text{OR}^2$, $-\text{R}^2$, $-\text{SO}_2\text{R}^2$, $-\text{SO}_2-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$, $-\text{R}^2-\text{OH}$, $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C}(\text{O})-\text{N}(\text{R}^2)_2$, halo, $-\text{CF}_3$;

each R^2 is independently selected from H , or C_1-C_4 alkyl; and wherein said alkyl, when not a substituent of Q , is optionally substituted with Q or $-\text{OR}^3$; wherein when said R^2 is an $-\text{OR}^3$ substituted moiety, said R^3 in $-\text{OR}^3$ may not be $-\text{OR}^2$ substituted;

B , when present, is $-\text{N}(\text{R}^2)-\text{C}(\text{R}^3)_2-\text{C}(\text{O})-$;

each x is independently 0 or 1;

each R^3 is independently selected from H , Ht , C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_5-C_6 cycloalkenyl; wherein any member of said R^3 , except H , is optionally substituted with one or more substituents selected from $-\text{OR}^2$, $-\text{C}(\text{O})-\text{NH}-\text{R}^2$, $-\text{S}(\text{O})_n-\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{O}(\text{R}^2)$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{N}(\text{R}^2)$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-(\text{R}^2)$, Ht , $-\text{CN}$, $-\text{SR}^2$, $-\text{CO}_2\text{R}^2$, or $\text{NR}^2-\text{C}(\text{O})-\text{R}^2$;

each n is independently 1 or 2;

G , when present, is selected from H , R^7 or C_1-C_4 alkyl, or, when G is C_1-C_4 alkyl, G and R^7 are optionally bound to one another either directly or through a C_1-C_3 linker to form a heterocyclic ring; or

when G is not present, the nitrogen to which G is attached is bound directly to the R⁷ group in -OR⁷ with the concomitant displacement of one -ZM group from R⁷;

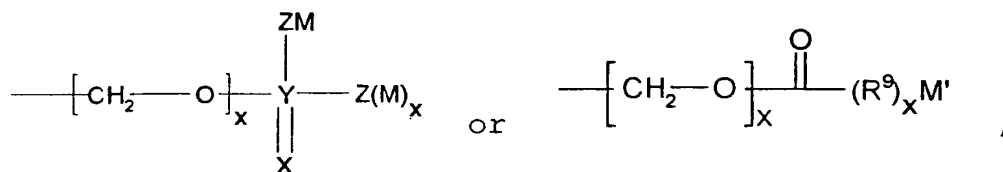
D is selected from Q; C₁-C₆ alkyl optionally substituted with one or more groups selected from C₃-C₆ cycloalkyl, -OR², -S-Ht, -R³, -O-Q or Q; C₂-C₄ alkenyl optionally substituted with one or more groups selected from -OR², -S-Ht, -R³, -O-Q or Q; C₃-C₆ cycloalkyl optionally substituted with or fused to Q; or C₅-C₆ cycloalkenyl optionally substituted with or fused to Q;

D' is selected from C₁-C₁₅ alkyl, C₂-C₁₅ alkenyl or C₂-C₁₅ alkynyl, each of which contains one or more substituents selected from oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CN, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -N(R³)-C(O)-S(R³), -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-S(O)_n-N(R³)₂, -S-NR³-C(O)R³, -C(S)N(R³)₂, -C(S)R³, -NR³-C(O)OR³, -O-C(O)OR³, -O-C(O)N(R³)₂, -NR³-C(S)R³, =N-OH, =N-OR³, =N-N(R³)₂, =NR³, =NNR³C(O)N(R³)₂, =NNR³C(O)OR³, =NNR³S(O)_n-N(R³)₂, -NR³-C(S)OR³, -NR³-C(S)N(R³)₂, -NR³-C[=N(R³)]-N(R³)₂, -N(R³)-C[=N-NO₂]-N(R³)₂, -N(R³)-C[=N-NO₂]-OR³, -N(R³)-C[=N-CN]-OR³, -N(R³)-C[=N-CN]-(R³)₂, -OC(O)R³, -OC(S)R³, -OC(O)N(R³)₂, -C(O)N(R³)-N(R³)₂, -O-C(O)N(R³)-N(R³)₂, O-C(O)N(OR³)(R³), N(R³)-N(R³)C(O)R³, N(R³)-OC(O)R³, N(R³)-OC(O)R³, N(R³)-OC(O)R³, -OC(S)N(R³)₂, -OC(S)N(R³)(R³), or PO₃-R³; with the proviso that when R⁷ is H, E' is -SO₂, G is H or alkyl, and when B is present or when B is not present and R¹ is -C(O)-, D' may not be C₁-C₁₅ alkyl substituted with one substituent selected from -N(R³)₂, -SR³ or -S(O)_n-R³, or substituted with two -N(R³)₂ substituents;

E is selected from Ht; O-Ht; Ht-Ht; Ht fused with Ht; $-O-R^3$; $-N(R^2)(R^3)$; C_1-C_6 alkyl optionally substituted with one or more groups selected from R^4 or Ht; C_2-C_6 alkenyl optionally substituted with one or more groups selected from R^4 or Ht; C_3-C_6 saturated carbocycle optionally substituted with one or more groups selected from R^4 or Ht; or C_5-C_6 unsaturated carbocycle optionally substituted with one or more groups selected from R^4 or Ht;

each R^4 is independently selected from $-OR^2$, $-OR^3$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-CO_2R^2$, $-C(O)-NHR^2$, $-C(O)-N(R^2)_2$, $-C(O)-NR^2(OR^2)$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, $-N(R^2)_2$ or $-CN$;

each R^7 is independently selected from hydrogen,



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group, other than the $-\text{CH}_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, $S(O)$, $S(O)_2$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH , $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R^2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3 , $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group is

optionally replaced by a heteroatom group selected from O, S, S(O), S(O)₂, or N(R²); and wherein any hydrogen in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -OR², -R², -N(R²)₂, N(R²)₃, -R²OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, -C(O)R², -S(O)_n-R², -OCF₃, -S(O)_n-R⁶, -N(R²)-S(O)₂(R²), halo, -CF₃, or -NO₂;

Z is O, S, N(R²)₂, or, when M is not present, H.

Y is P or S;

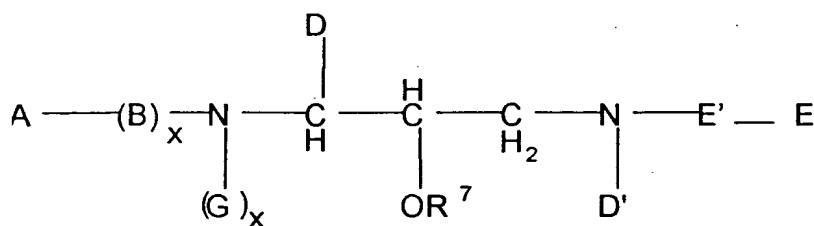
X is O or S;

R⁹ is C(R²)₂, O or N(R²); and wherein when Y is S, Z is not S;

R⁶ is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C₁-C₄ alkyl, -O-C₁-C₄ alkyl or -O-C(O)-C₁-C₄ alkyl; and

each R⁵ is independently selected from hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl or Ht, wherein any R⁵, except for hydrogen, is optionally substituted with -CF₃, -PO₃R³, azido or halo.

2. The compound according to claim 1, having the formula IA:



(IA)

wherein:

D' is selected from C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl or C_{2-C15} alkynyl; each of which is substituted with one to two -CN groups and each of which is optionally substituted with C_{3-C8} cycloalkyl.

3. The compound according to claim 2

wherein:

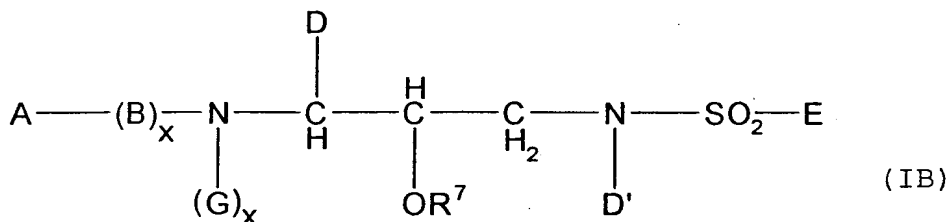
D' is selected from C₁₋₁₅ alkyl or C₂₋₁₅ alkenyl; each of which is substituted with one to two -CN groups and each of which is optionally substituted with C_{3-C8} cycloalkyl.

4. The compound according to claim 2

wherein:

D' is C_{2-C15} alkynyl which is substituted with one to two -CN groups and each of which is optionally substituted with C_{3-C8} cycloalkyl.

5. The compound according to claim 1 having the formula IB:



(IB)

wherein:

D' is selected from C₁-C₁₅ alkyl, C₂-C₁₅ alkenyl or C₂-C₁₅ alkynyl, each of which contains one or more substituents selected from oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -N(R³)-C(O)-S(R³), -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-S(O)_n-N(R³)₂, -S-NR³-C(O)R³, -C(S)N(R³)₂, -C(S)R³, -NR³-C(O)OR³, -O-C(O)OR³, -O-C(O)N(R³)₂, -NR³-C(S)R³, =N-OH, =N-OR³, =N-N(R³)₂, =NR³, =NNR³C(O)N(R³)₂, =NNR³C(O)OR³, =NNR³S(O)_n-N(R³)₂, -NR³-C(S)OR³, -NR³-C(S)N(R³)₂, -NR³-C[=N(R³)]-N(R³)₂, -N(R³)-C[=N-NO₂]-N(R³)₂, -N(R³)-C[=N-NO₂]-OR³, -N(R³)-C[=N-CN]-OR³, -N(R³)-C[=N-CN]-(R³)₂, -OC(O)R³, -OC(S)R³, -OC(O)N(R³)₂, -C(O)N(R³)-N(R³)₂, -O-C(O)N(R³)-N(R³)₂, O-C(O)N(OR³)(R³), N(R³)-N(R³)C(O)R³, N(R³)-OC(O)R³, N(R³)-OC(O)R³, N(R³)-OC(O)R³, -OC(S)N(R³)₂, -OC(S)N(R³)(R³), or PO₃-R³; with the proviso that when R⁷ is H, E' is -SO₂-, G is H or alkyl, and when B is present or when B is not present and R¹ is -C(O)-, D' may not be C₁-C₁₅ alkyl substituted with one substituent selected from -N(R³)₂, -SR³ or -S(O)_n-R³, or substituted with two -N(R³)₂ substituents.

6. The compound according to claim 5 wherein:

D' is selected from C₁-C₁₅ alkyl or C₂-C₁₅ alkenyl, each of which contains one or more substituents selected from oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -N(R³)-C(O)-N(R³)₂, -N(R³)-C(O)-S(R³), -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-

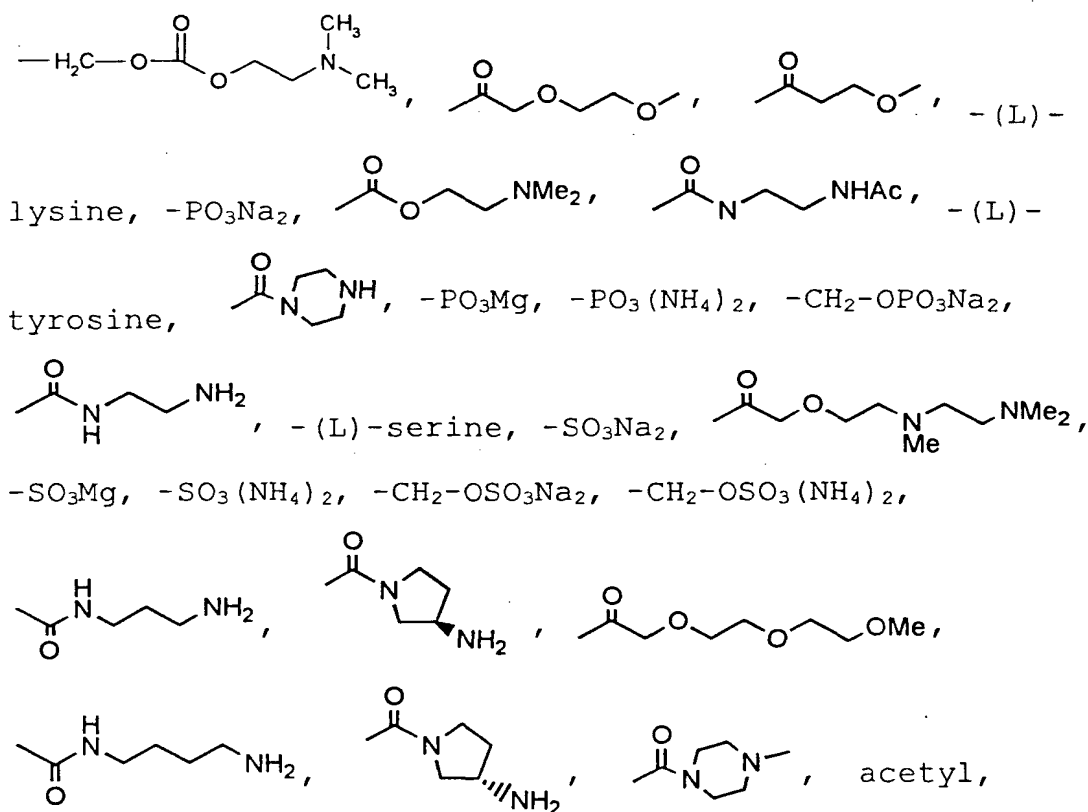
$S(O)_n-N(R^3)_2$, $-S-NR^3-C(O)R^3$, $-C(S)N(R^3)_2$, $-C(S)R^3$, $-NR^3-C(O)OR^3$, $-O-C(O)OR^3$, $-O-C(O)N(R^3)_2$, $-NR^3-C(S)R^3$, $=N-OH$, $=N-OR^3$, $=N-N(R^3)_2$, $=NR^3$, $=NNR^3C(O)N(R^3)_2$, $=NNR^3C(O)OR^3$, $=NNR^3S(O)_n-N(R^3)_2$, $-NR^3-C(S)OR^3$, $-NR^3-C(S)N(R^3)_2$, $-NR^3-C[=N(R^3)]-N(R^3)_2$, $-N(R^3)-C[=N-NO_2]-N(R^3)_2$, $-N(R^3)-C[=N-NO_2]-OR^3$, $-N(R^3)-C[=N-CN]-OR^3$, $-N(R^3)-C[=N-CN]-(R^3)_2$, $-OC(O)R^3$, $-OC(S)R^3$, $-OC(O)N(R^3)_2$, $-C(O)N(R^3)-N(R^3)_2$, $-O-C(O)N(R^3)-N(R^3)_2$, $O-C(O)N(OR^3)(R^3)$, $N(R^3)-N(R^3)C(O)R^3$, $N(R^3)-OC(O)R^3$, $N(R^3)-OC(O)R^3$, $N(R^3)-OC(O)R^3$, $-OC(S)N(R^3)_2$, $-OC(S)N(R^3)(R^3)$, or PO_3-R^3 ; C_2-C_{15} alkynyl which contains one or more substituents selected from oxo, halo, $-CF_3$, $-OCF_3$, $-NO_2$, azido, $-SH$, $-SR^3$, $-N(R^3)-N(R^3)_2$, $-O-N(R^3)_2$, $-(R^3)N-O-(R^3)$, $-N(R^3)_2$, $-CO_2R^3$, $-C(O)-N(R^3)_2$, $-S(O)_n-N(R^3)_2$, $-N(R^3)-C(O)-R^3$, $-N(R^3)-C(O)-N(R^3)_2$, $-N(R^3)-C(O)-S(R^3)$, $-C(O)-R^3$, $-S(O)_n-R^3$, $-N(R^3)-S(O)_n(R^3)$, $-N(R^3)-S(O)_n-N(R^3)_2$, $-S-NR^3-C(O)R^3$, $-C(S)N(R^3)_2$, $-C(S)R^3$, $-NR^3-C(O)OR^3$, $-O-C(O)OR^3$, $-O-C(O)N(R^3)_2$, $-NR^3-C(S)R^3$, $=N-OH$, $=N-OR^3$, $=N-N(R^3)_2$, $=NR^3$, $=NNR^3C(O)N(R^3)_2$, $=NNR^3C(O)OR^3$, $=NNR^3S(O)_n-N(R^3)_2$, $-NR^3-C(S)OR^3$, $-NR^3-C(S)N(R^3)_2$, $-NR^3-C[=N(R^3)]-N(R^3)_2$, $-N(R^3)-C[=N-NO_2]-N(R^3)_2$, $-N(R^3)-C[=N-NO_2]-OR^3$, $-N(R^3)-C[=N-CN]-OR^3$, $-N(R^3)-C[=N-CN]-(R^3)_2$, $-OC(O)R^3$, $-OC(S)R^3$, $-OC(O)N(R^3)_2$, $-C(O)N(R^3)-N(R^3)_2$, $-O-C(O)N(R^3)-N(R^3)_2$, $O-C(O)N(OR^3)(R^3)$, $N(R^3)-N(R^3)C(O)R^3$, $N(R^3)-OC(O)R^3$, $N(R^3)-OC(O)R^3$, $N(R^3)-OC(O)R^3$, $-OC(S)N(R^3)_2$, $-OC(S)N(R^3)(R^3)$, or PO_3-R^3 ; with the proviso that when R^7 is H, E' is $-SO_2-$, G is H or alkyl, and when B is present or when B is not present and R^1 is $-C(O)-$, D' may not be C_1-C_{15} alkyl substituted with one substituent selected from $-N(R^3)_2$ or $-S(O)_n-R^3$, or substituted with two $-N(R^3)_2$ substituents.

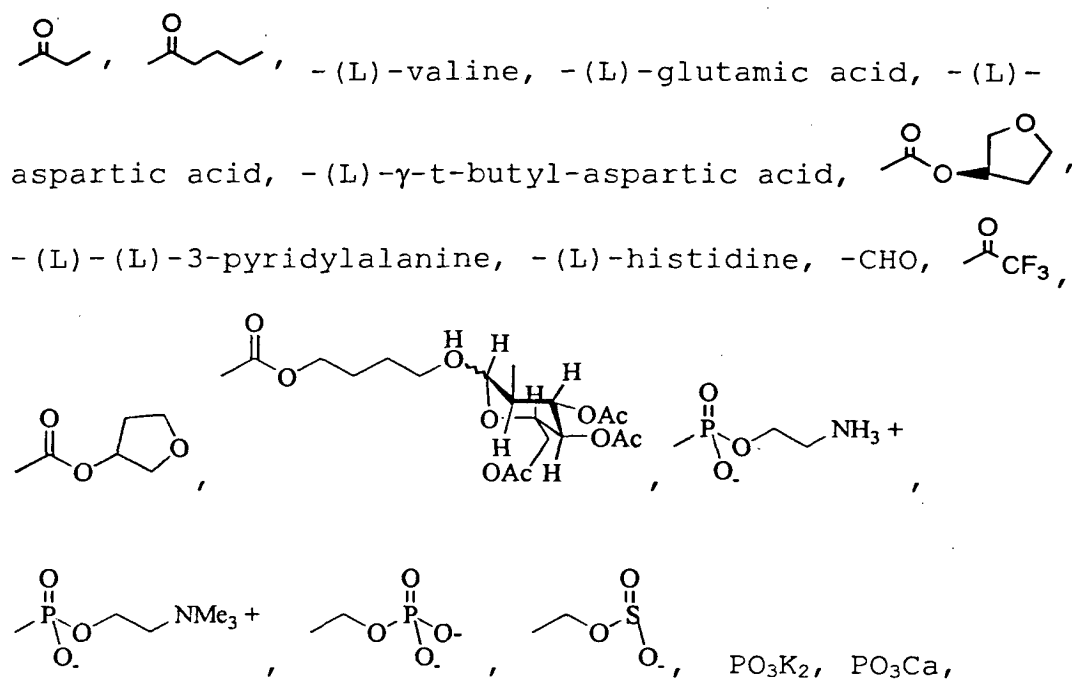
7. The compound according to claim 5 wherein:

D' is selected from C₁-C₁₅ alkyl or C₂-C₁₅ alkenyl, each of which contains one or more substituents selected from -SH, -SR³, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂ or -N(R³)-C(O)-R³; with the proviso that when R⁷ is H, E' is -SO₂-, G is H or alkyl, and when B is present or when B is not present and R¹ is -C(O)-, D' may not be C₁-C₁₅ alkyl substituted with one substituent selected from -SR³.

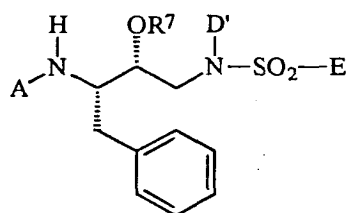
8. The compound according to any one of claims 1 to 4, wherein E' is SO₂.

9. The compound according to any one of claims 1 to 7, wherein at least one R⁷ is selected from:




$$\text{PO}_3\text{-spermine, PO}_3\text{-(spermidine)}_2 \text{ or PO}_3\text{-(meglamine)}_2.$$

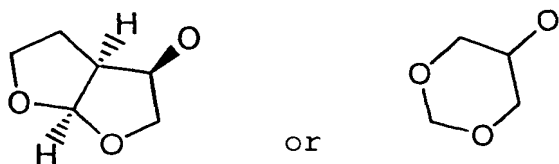
10. The compound according to claim 8, having the formula II:



(II) .

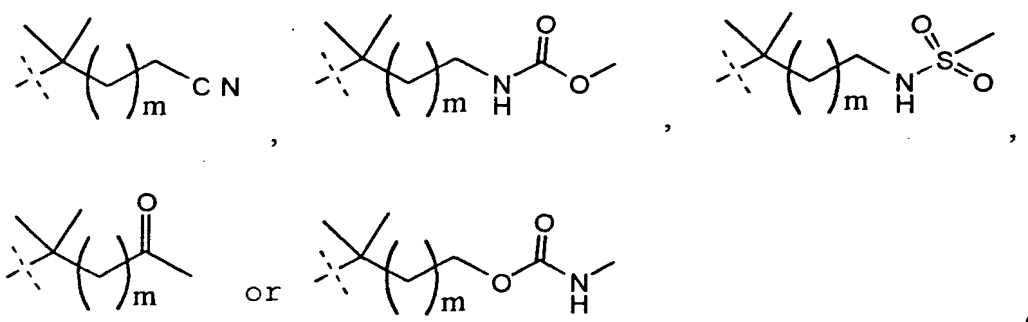
11. The compound according to claim 10,
wherein:

A is R'-C(O)-; and
R' is selected from



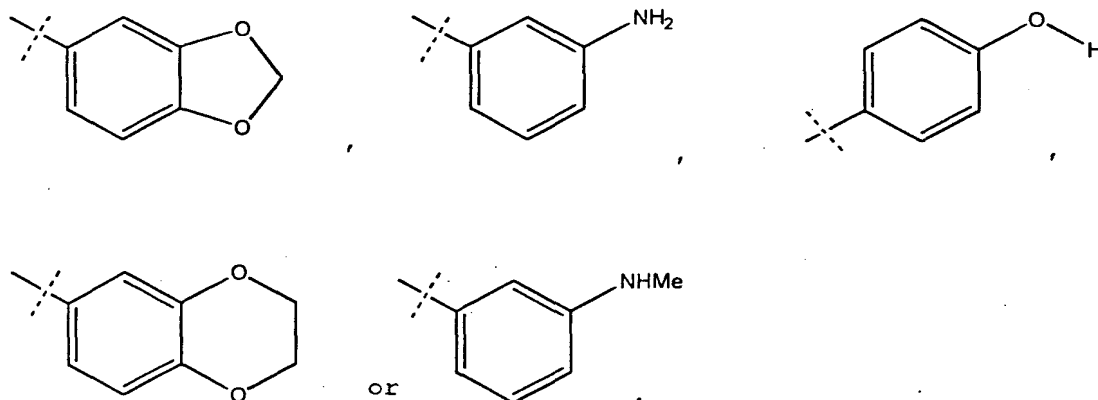
12. The compound according to claim 10,
wherein:

D' is $-\text{CH}_2-\text{R}''$; and
R'' is selected from



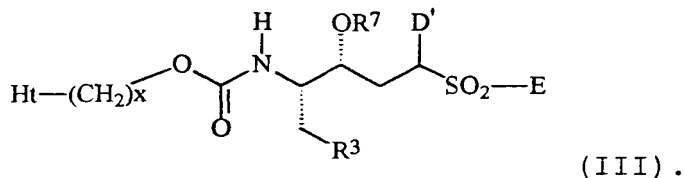
wherein m is 0 to 3.

13. The compound according to claim 10,
wherein E is selected from

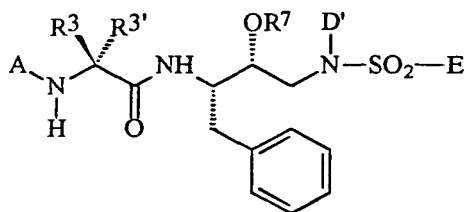


14. The compound according to claim 10,
wherein R⁷ is $-\text{PO}_3^{2-}$.

15. The compound according to claim 1, having the formula III:



16. The compound according to claim 1, having the formula IV:



wherein $R^{3'}$ is selected from H, Ht, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 cycloalkyl or C_5 - C_6 cycloalkenyl; wherein any member of said R^3 , except H, is optionally substituted with one or more substituents selected from $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, $-N(R^2)_2$, $-N(R^2)-C(O)-O(R^2)$, $-N(R^2)-C(O)-N(R^2)$, $-N(R^2)-C(O)-(R^2)$, $-N(R^2-OR^2)_2$, $-C(O)-Ht$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$, or $NR^2-C(O)-R^2$.

17. The compound according to claim 11, wherein said compound is selected from any one of compound numbers: 210, 224, 240, 248, 250, 255, 263, 270, 272, 280, 299, 300, 307, 309, 313, 314, 315, 316, 359, 360, 384, 483, 494, 496, 523, 524, 531, 542, 548, 553, 558, 563, 570, 571, 575, 579, 589, 596, 606, 609, 616.

18. The compound according to claim 11, wherein said compound is selected from any one of

compound numbers: 12, 16, 25, 29, 30, 31, 35, 39, 41, 42, 47, 100, 124, 375, 378, 421, 459, 464.

19. The compound according to claim 17, wherein said compound is selected from any one of compound numbers: 224, 240, 263, 270, 272, 280, 299, 300, 307, 309, 313, 314, 315, 316, 359, 360, 384, 483, 494, 496, 548, 553, 558, 563, 570, 571, 575, 579, 589, 596, 606, 609, 616.

20. The compound according to claim 18, wherein said compound is selected from any one of compound numbers: 12, 16, 25, 35, 39, 42, 47, 100, 375, 378, 421, 459, 464.

21. The compound according to claim 19, wherein said compound is selected from any one of compound numbers: 224, 240, 272, 299, 314.

22. The compound according to claim 20, wherein said compound is selected from any one of compound numbers: 16, 25, 42, 47, 100.

23. A composition comprising a compound according to any one of claims 1-22 or a pharmaceutically acceptable salt thereof in an amount sufficient to detectably inhibit aspartyl protease activity in a patient, and a pharmaceutically acceptable carrier.

24. The composition according to claim 23, further comprising an additional antiviral agent other than a compound of formula (I).

25. The composition according to claim 23, wherein said composition is formulated as a pharmaceutically acceptable, orally available tablet or capsule.

26. A method of treating an HIV virus infection in a human comprising the step of administering to said human a composition according to any one of claims 23 to 25.

27. The method according to claim 26, comprising the step of administering to said patient an additional antiviral agent other than a compound of formula I, wherein said additional antiviral agent is administered prior to, simultaneously with or following administration of said composition.